# ANHYDROUS NITRONIUM TRIFLATE NITRATION OF AROMATIC and HETEROAROMATIC COMPOUNDS: CONVENTIONAL BENCHTOP & MICROWAVE-ASSISTED CONDITIONS

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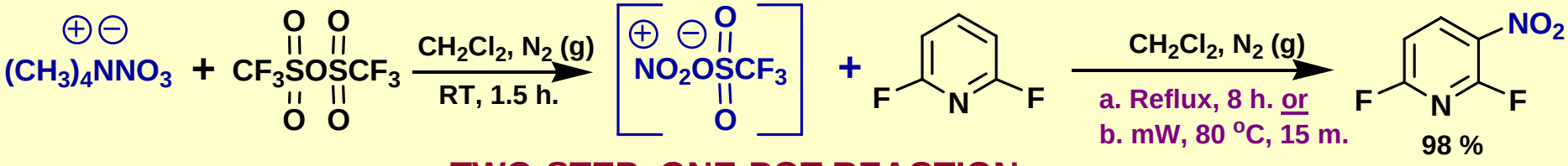


**TWO-STEP, ONE-POT REACTION**



**POSTPRINT**

# Report Documentation Page

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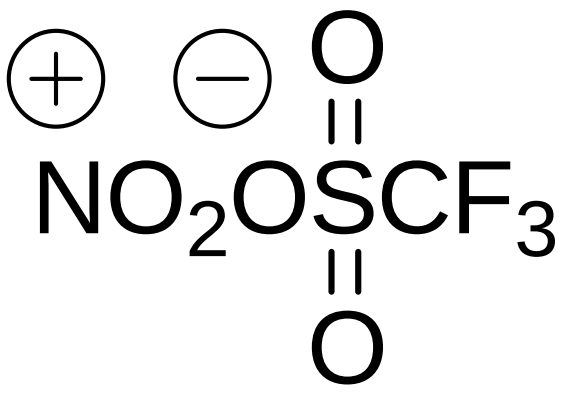
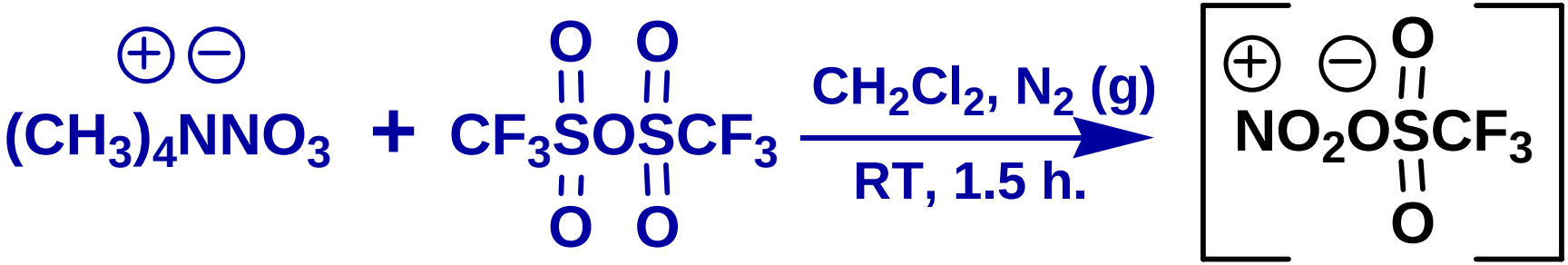
# ANHYDROUS NITRONIUM TRIFLATE NITRATION



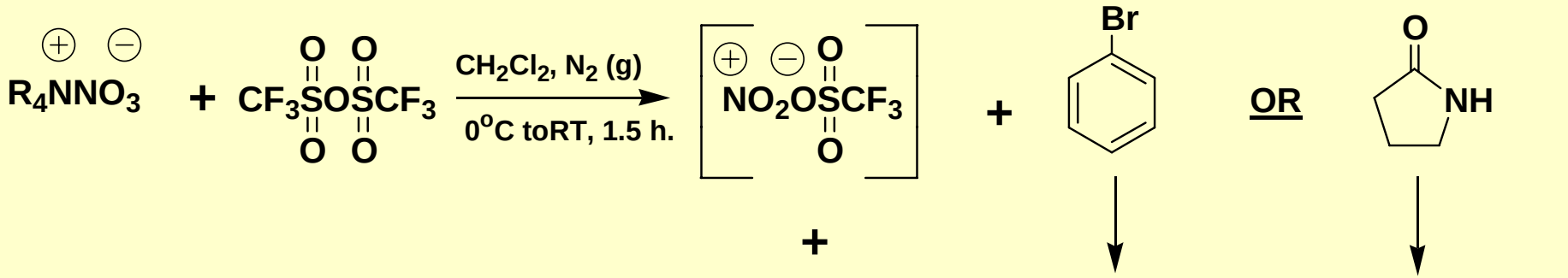
## CONVENIENT IN-SITU GENERATION



# OVERVIEW

- IMPROVED $NO_2OSO_2CF_3$ NITRATING REAGENT *IN-SITU* FORMATION
  - $(n\text{-Bu})_4NNO_3$ GENERATED REAGENT
  - $(CH_3)_4NNO_3$ GENERATED REAGENT
- CONVENTIONAL BENCHTOP & MICROWAVE-ASSISTED $NO_2OSO_2CF_3$ NITRATION RESULTS
  - CONVENTIONAL BENCHTOP LIMITATIONS
  - MICROWAVE-ASSISTED EXTENTIONS
- PRELIMINARY MICROWAVE-ASSISTED $NO_2OSO_2CF_3$ NITRATION SCREENING REACTIONS
  - DIRECTIONAL EFFECTS OF 5-MEMBERED HETEROAROMATICS
  - POSITIONAL NITRATION REACTIVITY

# ANHYDROUS NITRONIUM TRIFLATE NITRATION




R = -*n*-Bu
-$CH_2CH_3$

$CH_2Cl_2$ SOLUBLE
COLUMN CHROMATOGRAPHY [1,2]

R = $-CH_3$

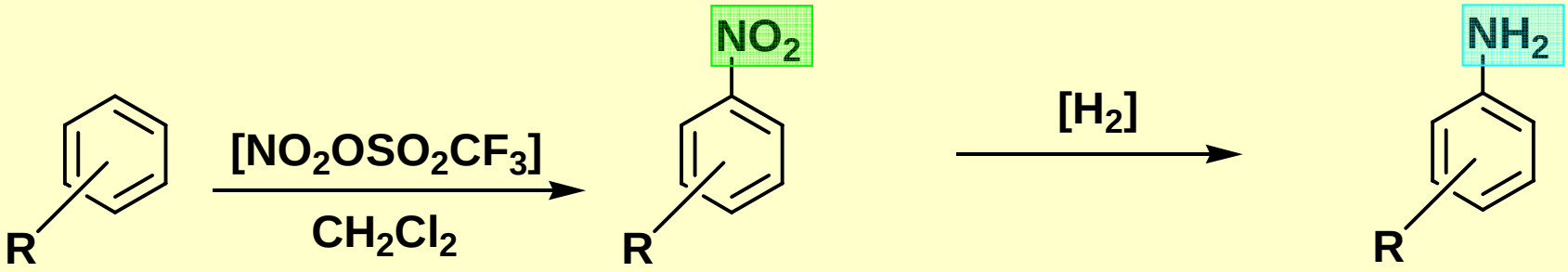
$H_2O$ SOLUBLE
AQUEOUS WORK-UP ONLY

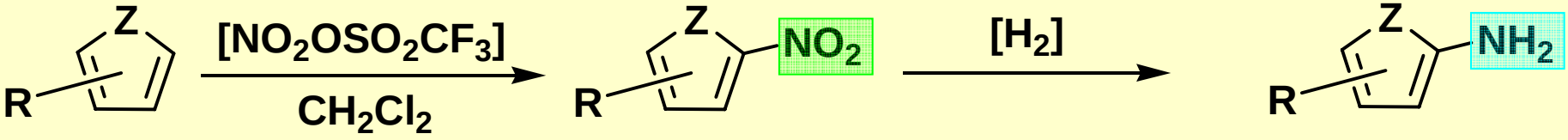
$H_2O$ SOLUBLE


1. Shackelford, S. A.; Adams, C. M.; Sharts, C. M. 11th Rocky Mountain Region ACS Mtg., Albuquerque, NM, 10-12 Jul 1992.
2. Adams, C. M.; Sharts, C. M.; Shackelford, S. A. *Tetrahedron Lett.* **1993**, *34*, 6669-6671.

# ANHYDROUS NITRONIUM TRIFLATE NITRATION

## OBJECTIVE: NEW AROMATICS & HETEROAROMATICS



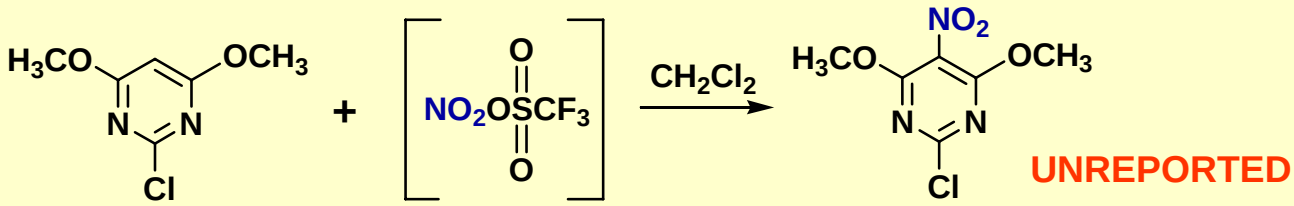




Z = C, O, N, S

NEW NITRATED COMPOUNDS

NEW AMINO-SYNTHONS

# ANHYDROUS NITRONIUM TRIFLATE NITRATION

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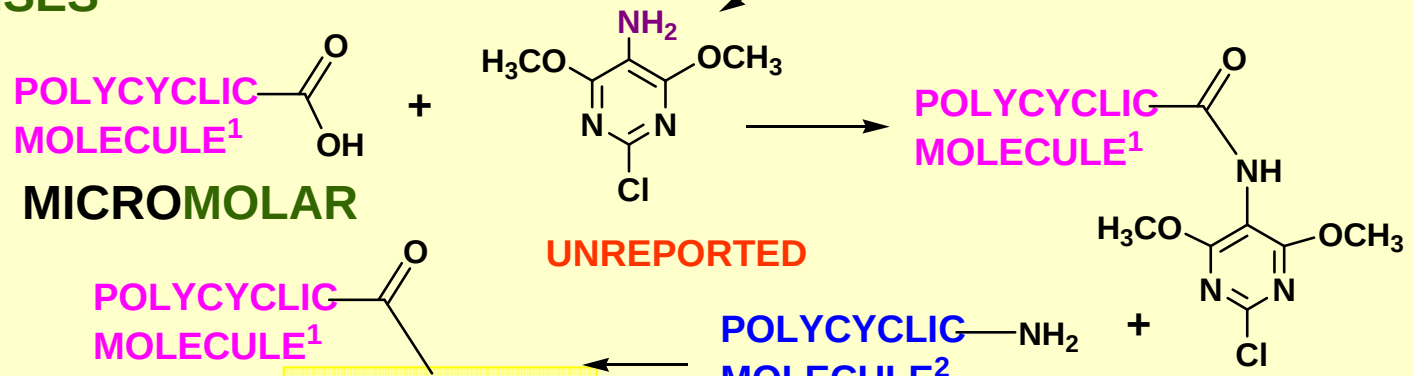
**BIOASSY RESPONSES**

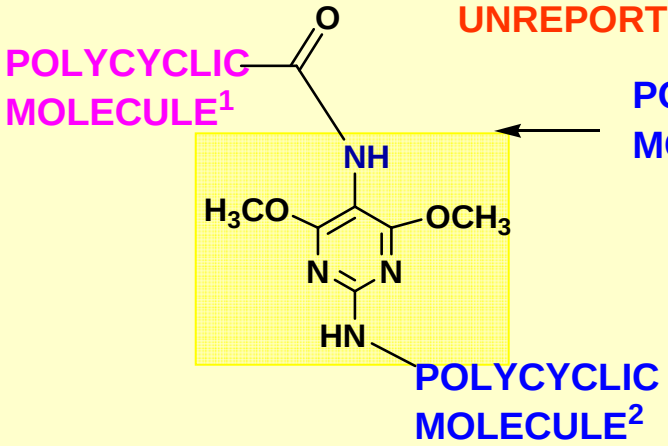
$[H_2]$




**MICROMOLAR**

UNREPORTED

**NANOMOLAR**

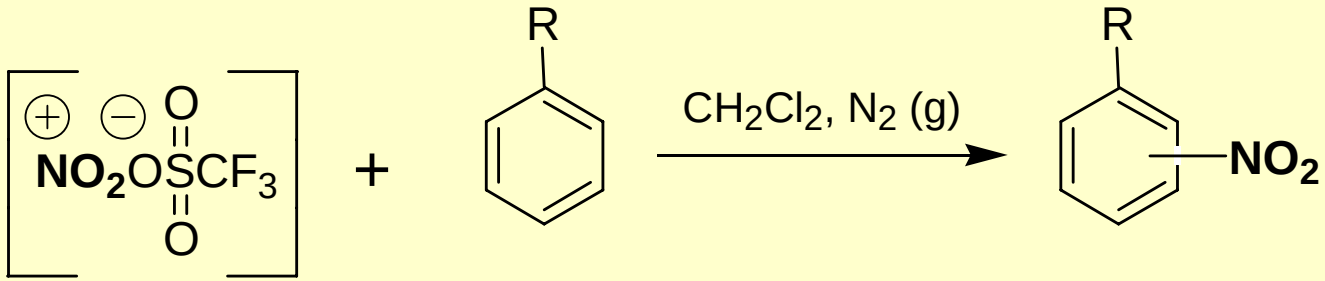



**PICOMOLAR**

**7 PHARMACEUTICAL CANDIDATES**

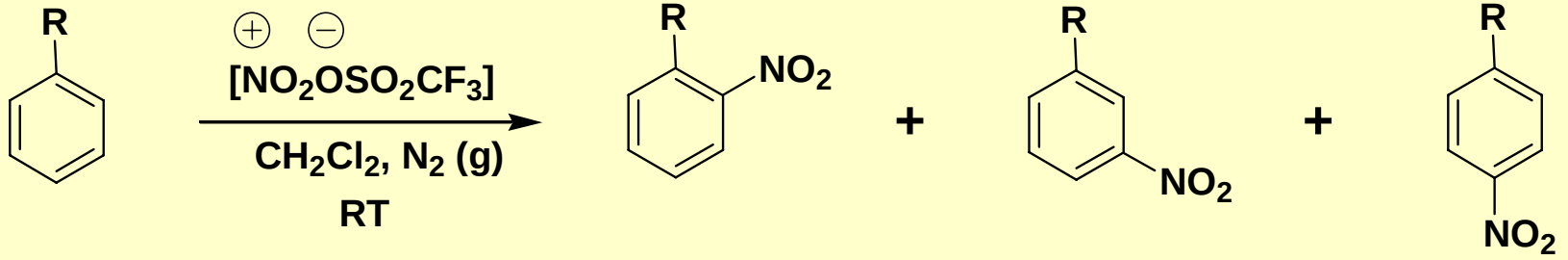
# ANHYDROUS NITRONIUM TRIFLATE NITRATION

## ➢ NITRATION CONDITIONS:

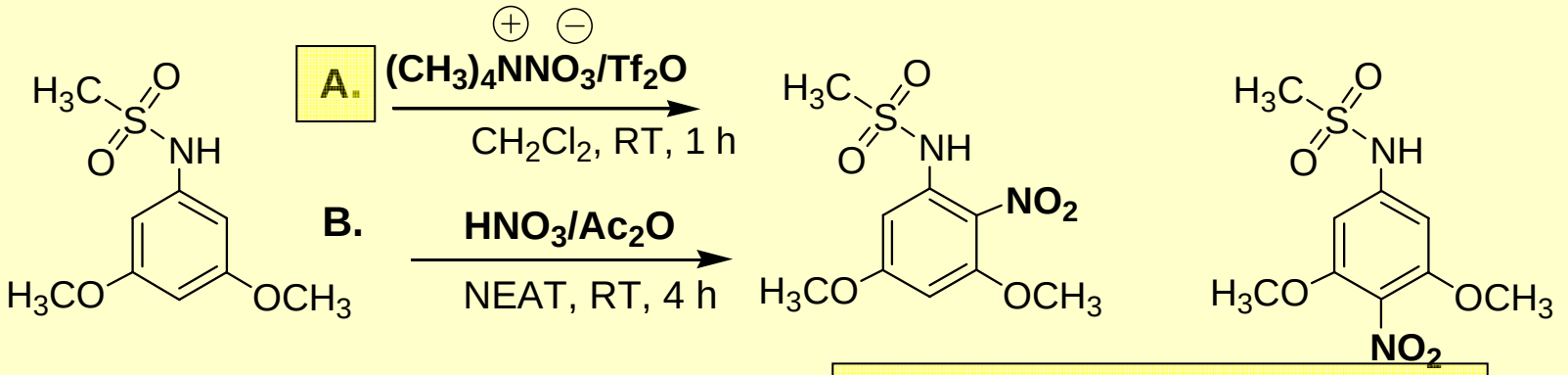



| | EQUIVALENTS | CONCENTRATION | TEMPERATURE | METHOD |
|---|---|---|---|---|
| **DILUTE:** | 1.05 to 1.7 | 0.2 to 0.3M | -78 °C to RT | CONVENTIONAL BENCHTOP |
| **CONC.:** | 1.5 to 2.0 | 1.1 to 3.6M | RT to >REFLUX | CONVENTIONAL BENCHTOP & MICROWAVE-ASSISTED |

# CONVENTIONAL BENCHTOP NITRONIUM TRIFLATE NITRATION



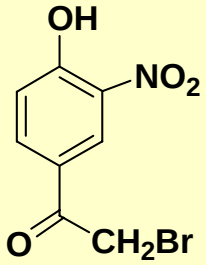
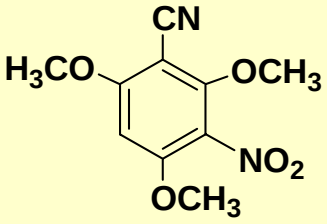
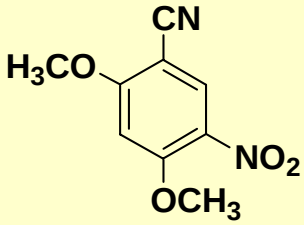
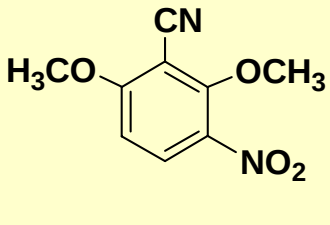
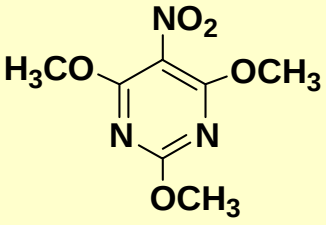

| R = | -ortho | -meta | -para |
|---|---|---|---|
| $-OCH_3$ | 63% | 5% | 32% |
| -OH | 90 | 0 | 10 |
| $-CH_3$ | 62 | 0 | 38 |
| -Br | 33 | 0 | 67 |
| $-CO_2H$ | 16 | 78 | 6 |
| $-CF_3$ | 8% | 88% | 4% |



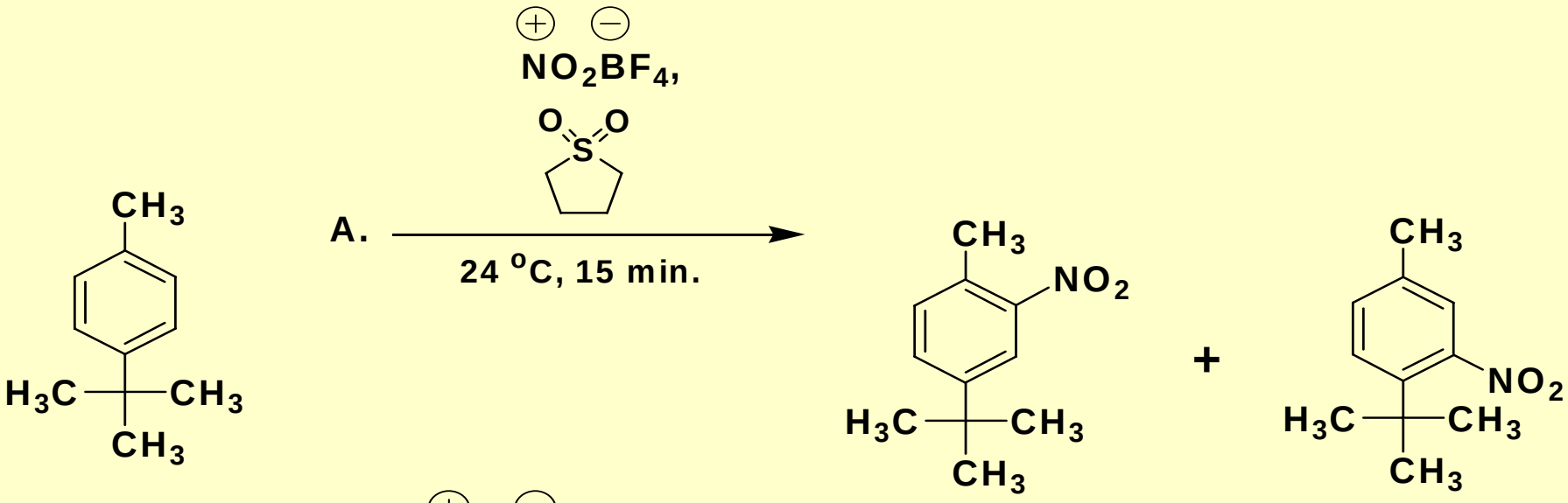

| | ortho | para |
|---|---|---|
| A. | 95% | 5% |
| B. | 0% | 100% |

# CONVENTIONAL BENCHTOP NITRONIUM TRIFLATE NITRATION

## ➢ NITRATION RESULTS:

| PRODUCT: |  |  |  |  |  |
|---|---|---|---|---|---|
| | | UNREPORTED | ONLY ISOMER | | DIRECT NITRATION |
| SCALE (mmol): | 8 93 | 8 100 | 100 | 100 | 371 |
| ISOLATED YIELD: | 94% 91% | 86% 82% | 91% | 100% | 82% |
| PURITY: | 91% 88% | 95% 95% | 82% | 97% | 98% |

## ➢ NITRATION SELECTIVITY (82 mmol):

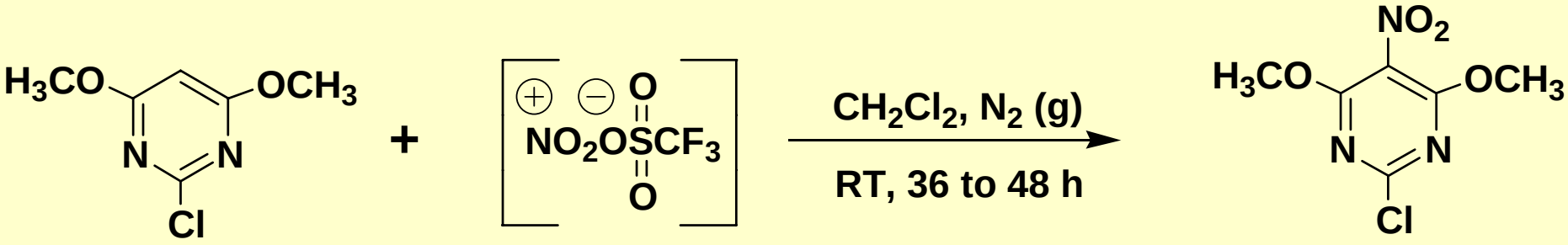



| | | |
|---|---|---|
| A. | 95% | 5%* |
| B. | 100% | 0% |
| B. | YIELD = 94%<br>PURITY = 93% | |

* Olah, G. A.; Kuhn, S. *J. Am. Chem. Soc.*, **1964**, *86*, 1067-1070.

# CONVENTIONAL BENCHTOP NITRONIUM TRIFLATE NITRATION

## ➢ $NO_2OSO_2CF_3$ EQUIVALENTS & NITRATION SCALE-UP:



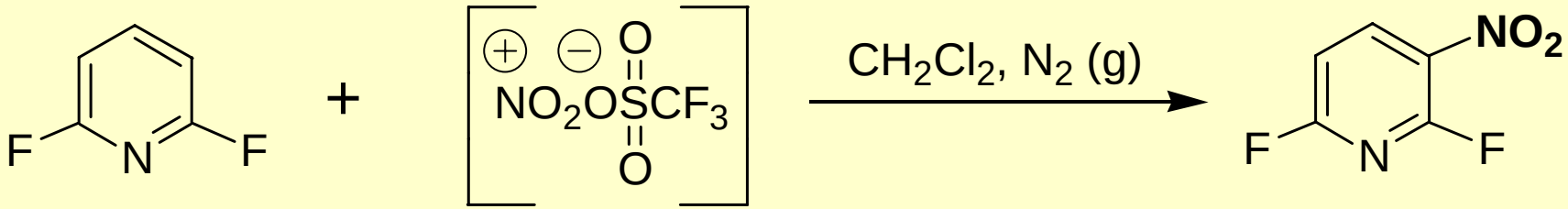

UNREPORTED

| CONDITIONS | SCALE (mmol) | $NO_2OSO_2CF_3$ EQUIV. | % CONVERTED | ISOLATED YIELD. | PURITY |
|---|---|---|---|---|---|
| [0.2M], 48 h | 8 | 1.05 | 68 | --------- | 68% |
| | 8 | 1.25 | 88 | --------- | 88% |
| | 8 | 1.50 | 100 | 98% | 99%* |
| [3.6M], 36 h | 2864 | 1.5 | 100 | 94% | >95% |

*ANALYTICALLY PURE BY C, H, Cl, and N, ELEMENTAL ANALYSES

# CONVENTIONAL BENCHTOP NITRONIUM TRIFLATE NITRATION

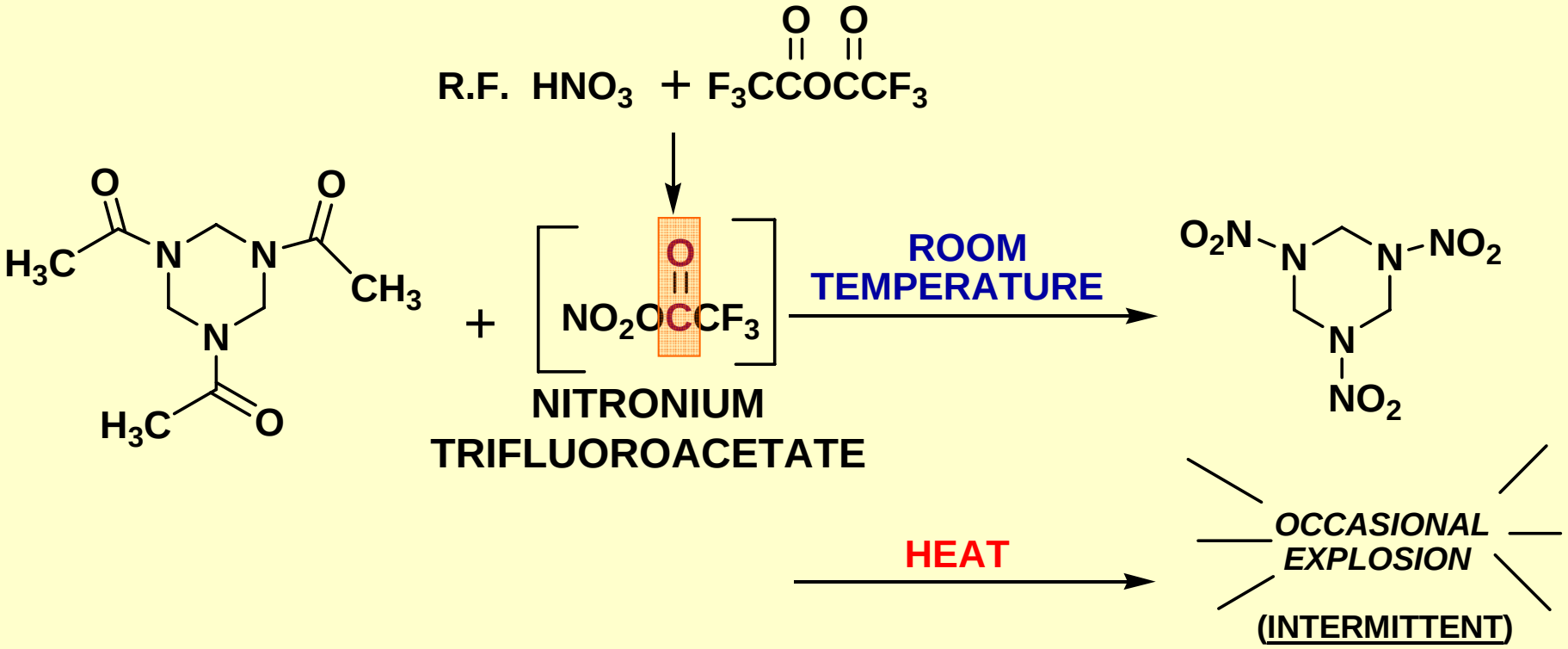
## ➢ NITRATION REACTIVITY:




| CONDITIONS | $NO_2OSO_2CF_3$ EQUIV. | [REACTANT CONC.] | % CONVERTED | ISOLATED YIELD | PURITY |
|---|---|---|---|---|---|
| RT, 42 h | 1.6 | 0.25M | 69% | -------- | <69% |
| RT, 24 h | 1.5 | 1.09M | 78% | -------- | 78% |

# CONVENTIONAL BENCHTOP NITRONIUM TRIFUOROACETATE NITRATION

## ➢ OTHER NITRATION REAGENT REACTIVITY:



# MICROWAVE-ASSISTED NITRONIUM TRIFLATE NITRATION

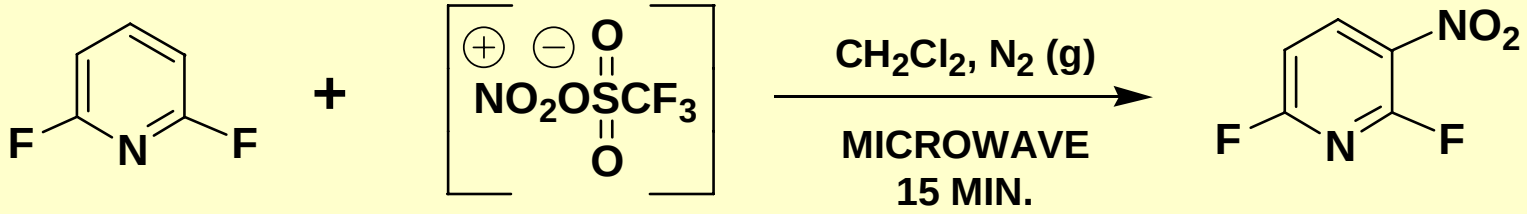
- **ORIGINAL MICROWAVE INSTRUMENTS EMPLOYED:**
  - **PERSONAL MICROWAVE™**
  - **MILESTONE ETHOS™**

**SMALL SCALE REACTIONS**
**3.4 mmol (0.5 gram)**

**LARGER-SCALE REACTIONS**
**54.5 mmol (10 grams)**

# MICROWAVE-ASSISTED NITRONIUM TRIFLATE NITRATION

## ➢ MICROWAVE TEMPERATURE SCREENING:



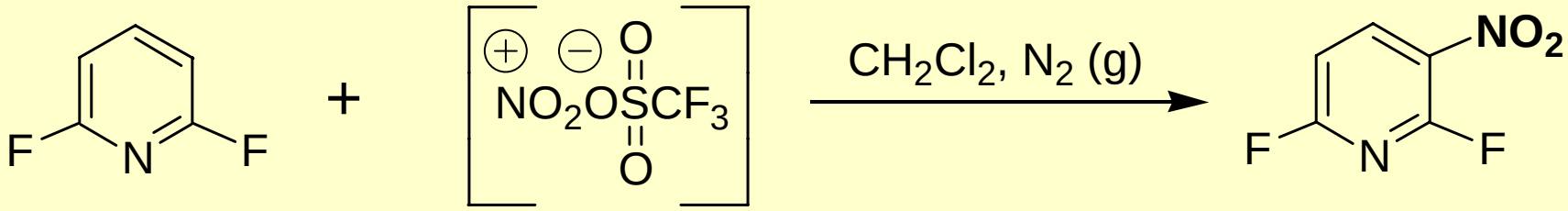

| RUN NO. | $NO_2OSO_2CF_3$ EQUIV. | TEMP (°C) | % CONVERTED | ISOLATED YIELD | PURITY |
|---|---|---|---|---|---|
| 1 | 1.3 | 60 | 91 | ------- | ------- |
| 8 | 1.5 | 60 | 96 | 85% | ------- |
| 5 | 1.5 | 110 | 100 | 91% | 98% |
| 7 | 1.5 | 100 | 100 | 91% | 98% |
| 9 | 1.5 | 80 | 100 | 94% | 100%* |

*ANALYTICALLY PURE BY C, H, F, & N ELEMENTAL ANALYSIS

- INCREASED $NO_2OSO_2CF_3$ EQUIVALENTS IMPROVE REACTANT CONVERSION (RUNS 1 & 8)
- INCREASED TEMPERATURE RAISES REACTANT CONVERSION (RUN 5)
- MINIMUM TEMPERATURE (80 °C) EXISTS FOR COMPLETE REACTION (RUN 9)

# CONVENTIONAL BENCHTOP NITRONIUM TRIFLATE NITRATION

## ➢ REFLUX TEMPERATURE NITRATION:

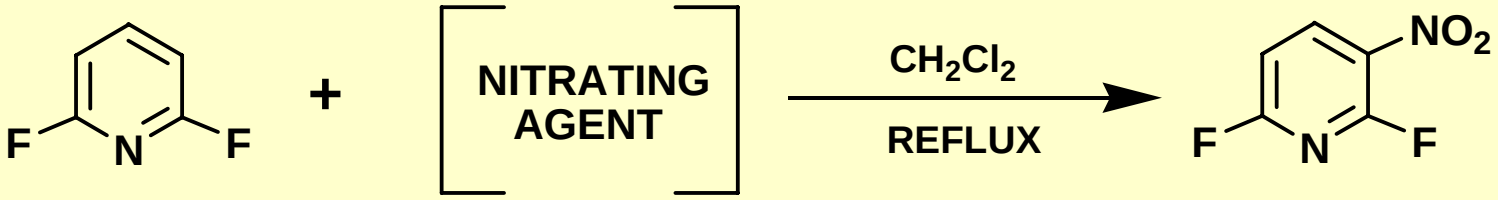



| CONDITIONS | $NO_2OSO_2CF_3$ EQUIV. | [REACTANT CONC.] | % CONVERTED | ISOLATED YIELD | PURITY |
|---|---|---|---|---|---|
| RT, 42 h | 1.6 | 0.25M | 69% | -------- | <69% |
| RT, 24 h | 1.5 | 1.09M | 78% | 98% | 78% |
| REFLUX, 8 h | 1.5 | 1.09M | 100% | 98% | 99%* |

*ANALYTICALLY PURE BY C, H, F, and N, ELEMENTAL ANALYSES

# CONVENTIONAL BENCHTOP NITRONIUM TRIFLATE NITRATION

## ➢ $NO_2OSO_2CF_3$ NITRATION EFFECTIVENESS:




| | TIME (h) | ISOLATED YIELD | PURITY |
|---|---|---|---|
| [$NO_2BF_4$ [A] ] | 24 | 20% | ------ |
| [$NO_2OSO_2CF_3$] | 8 | 98% | 99%* |

*ANALYTICALLY PURE BY C, H, F, and N ELEMENTAL ANALYSES

| | | | |
|---|---|---|---|
| [ $HNO_3$ (100%) / $H_2SO_4$ [B]] | 23 | 78%[C] | ------ |

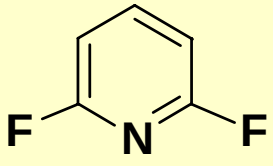
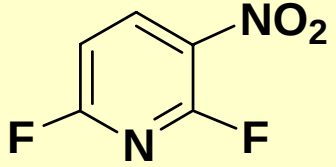
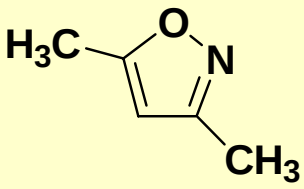
[B] NEAT, 0 °C to RT [C] DISTILLED YIELD


**A.** Duffy, J. L.; Laali, K. K. *J. Org. Chem*. **1991**, *56*, 3006-3009.

**B.** Mutterer, F.; Weiss, C. D. *Helv. Chem. Acta* **1976**, *59*, 229-235.

# CONVENTIONAL BENCHTOP NITRONIUM TRIFLATE NITRATION

## ➢ REFLUX REACTION TIMES:

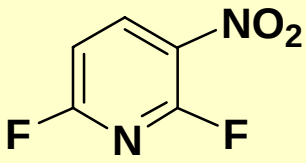
| REACTANT | TIME (h) | ISOLATED YIELD | PURITY | PRODUCT |
|---|---|---|---|---|
|  | 8* | 98% | 99%** |  |
| | 24 | 94% | 99%** | |
|  | 3.5 | 92% | 95% |  |
| | 16 | 90% | 95% | |

* MINIMUM REACTION TIME

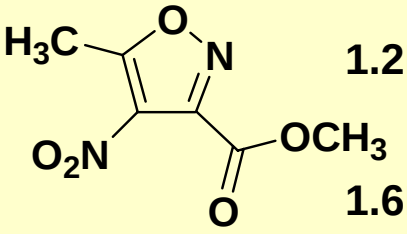
**ANALYTICALLY PURE BY C, H, F, and N ELEMENTAL ANALYSES

# CONVENTIONAL VS. MICROWAVE $NO_2OSO_2CF_3$ NITRATION COMPARISON

## ➢ COMPARATIVE PRODUCT RESULTS:




| CONC. | CONDITIONS | SCALE (mmol) | ISOLATED YIELD | PURITY |
|---|---|---|---|---|
| 1.2M | PERSONAL MICROWAVE 80 $^0$C, 15 min. | 3.4 | 94% | 100%* |
| 1.3M | MILESTONE MICROWAVE 80 $^o$C, 15 min. | 54.5 | 98% | 98%* |
| 1.1M | CONVENTIONAL BENCHTOP REFLUX, 8 h | 16.4 | 98% | 99%* |



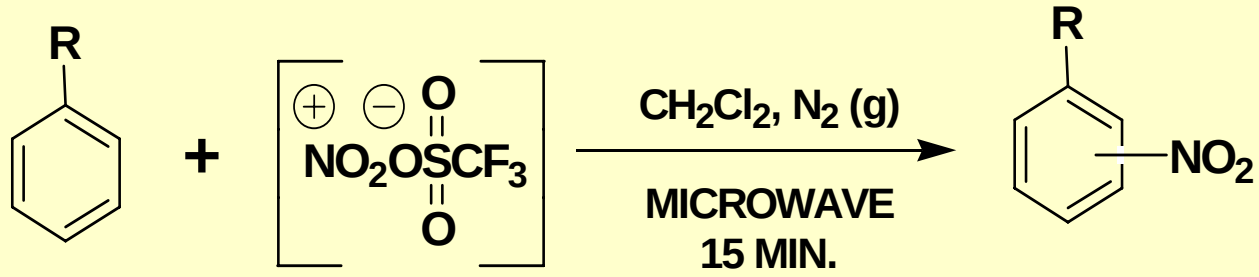

UNREPORTED

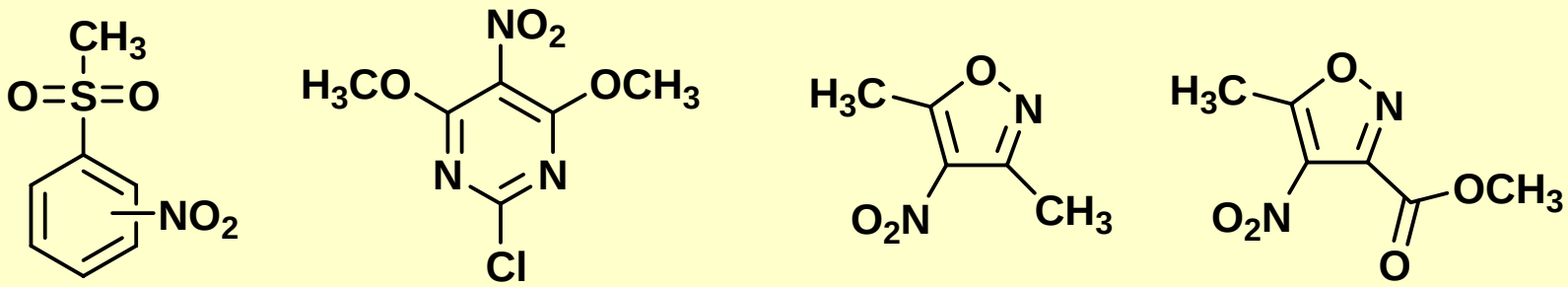
| | | | | |
|---|---|---|---|---|
| 1.2M | PERSONAL MICROWAVE 60 $^o$C, 15 min. | 3.4 | 100% | 99%* |
| 1.6M | MILESTONE MICROWAVE 60 $^o$C, 15 min. | 27.0 | 100% | 99%* |
| 1.2M | CONVENTIONAL BENCHTOP REFLUX, 24 h | 17.2 | 100% | 99%** |

*ANALYTICALLY PURE **ELEMENTAL ANALYSIS NOT CONDUCTED

# MICROWAVE-ASSISTED NITRONIUM TRIFLATE NITRATION

## ➢ MICROWAVE-ASSISTED PRODUCT RESULTS:



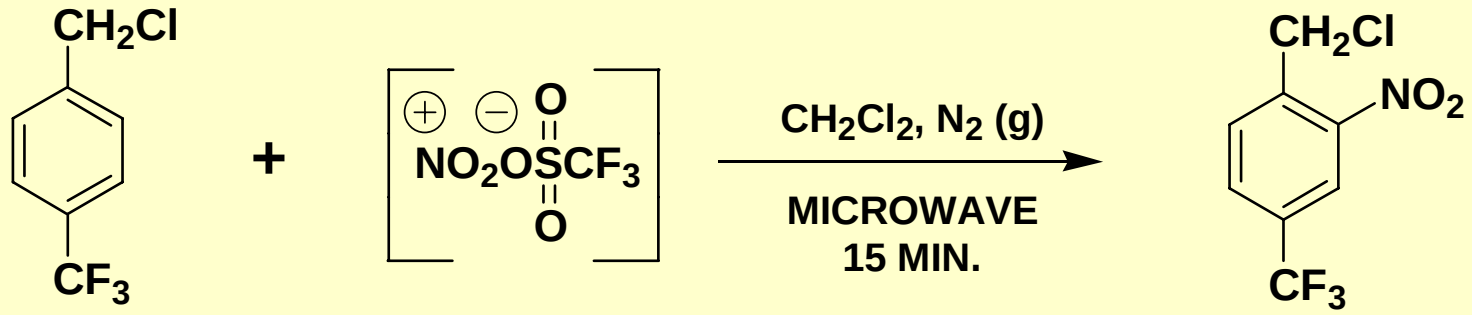




| | | | | |
|---|---|---|---|---|
| TEMP.(°C) | 80 | 60 | 60 | 60 |
| ISOLATED YIELD | 94% (*O/M/P* = 17/79/4) | 91% | 92% | 100% |
| PURITY | 100%* | 100%** | 100%** | 100%** |

*ISOMERIC MIXTURE ANALYTICALLY PURE **ANALYTICALLY PURE

# MICROWAVE-ASSISTED NITRONIUM TRIFLATE NITRATION

## ➢ MICROWAVE-ASSISTED PRODUCT RESULTS:

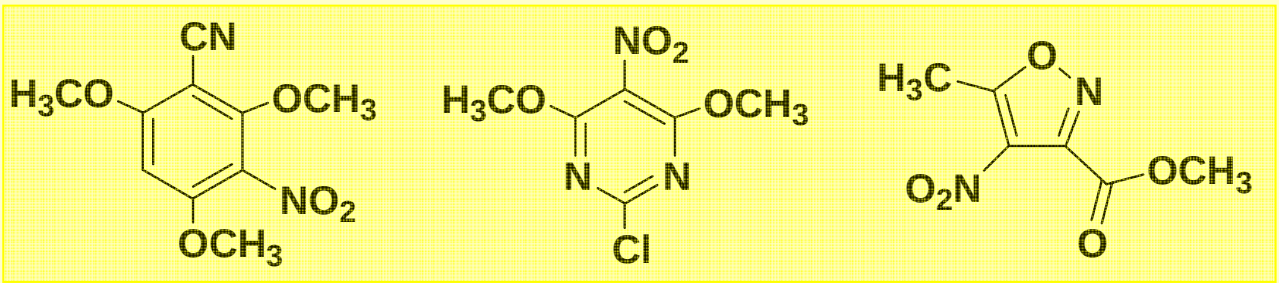


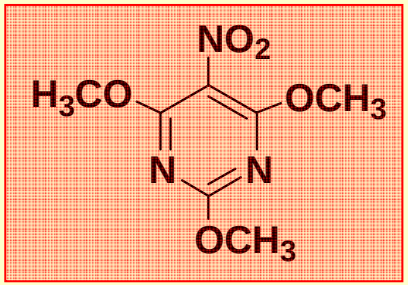

| RUN NO. | $NO_2OSO_2CF_3$ EQUIV. | TEMP (°C) | % CONVERTED | ISOLATED YIELD | PURITY |
|---|---|---|---|---|---|
| 1 | 1.5 | 80 | 82 | ------- | ----- |
| 2 | 1.5 | 100 | 82 | ------- | ----- |
| 3 | 2.0 | 80 | 100 | 98% | 95% |

- MINIMUM CONVERSION TEMPERATURE AT LEAST 80 °C (RUNS 1 & 2)
- $NO_2OSO_2CF_3$ EQUIVALENT INCREASE NEED FOR COMPLETE CONVERSION (RUN 3)

# MICROWAVE & CONVENTIONAL $NO_2OSO_2CF_3$ NITRATION

- **$(CH_3)_4NNO_3$ BASED NITRONIUM TRIFLATE NITRATION:**
  - **SIMPLE & CONVENIENT REACTION METHOD**
    - ✓ ONE-POT REACTION
    - ✓ EASY AQUEOUS WORK-UP
    - ✓ ISOMERIC SELECTIVITY
    - ✓ EXCELLENT PRODUCT YIELDS
    - ✓ HIGH (ANALYTICAL) "CRUDE" PRODUCT PURITY
    - ✓ DIRECTLY SCALEABLE
  - **NEW COMPOUNDS & NEW SYNTHESIS ROUTE (DIRECT NITRATION)**



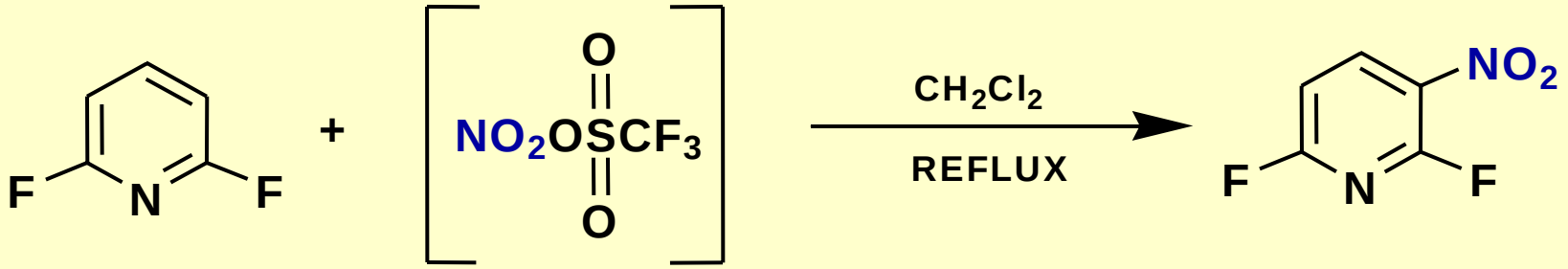

**Shackelford, S. A.; Anderson, M. B.; Christie, L. C.; Goetzen, T.; Guzman, M. C.; Hananel, M. A.; Kornreich, W. D.; Haitao, L.; Pathak, V. P.; Rabinovich, A. K.; Rajapakse, R. J.; Truesdale, L. K.; Tsank, S. M.; Vazir H. N.**
*J. Org. Chem.,* **2003,** *68*, 267-275.

# MICROWAVE NITRONIUM TRIFLATE SCREENING REACTIONS

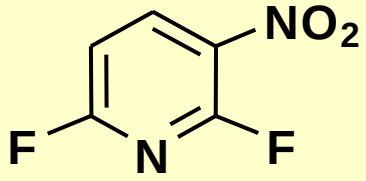
## BIOTAGE MICROWAVE INITIATOR™

# MICROWAVE NITRONIUM TRIFLATE SCREENING REACTIONS

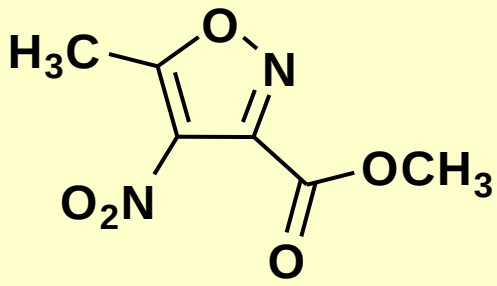
## ➢ MINIMUM NITRATION REACTION TIME:




| TEMP. | TIME (MIN) | PRODUCT CONVERSION |
|---|---|---|
| *MW SET* | 2 | 79% |
| = 80°C | 3 | 98% (2 RUNS) |
| *ACTUAL* | 4 | 100% |
| = 98-80°C | | |



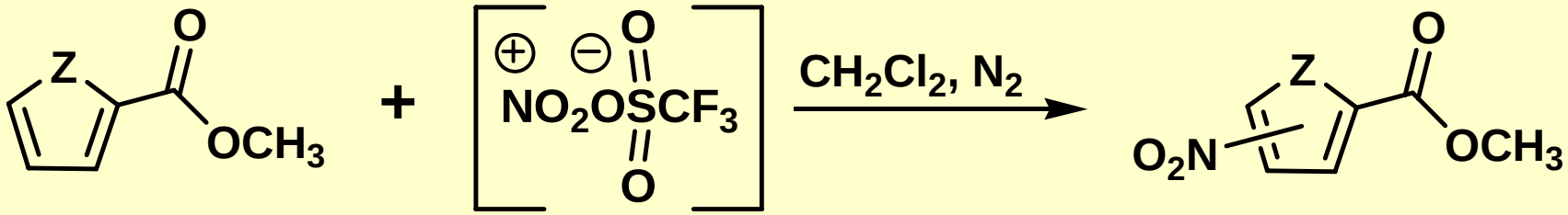

| | | |
|---|---|---|
| *MW SET* | 3 | 93% |
| = 60°C | 5 | 100% |
| *ACTUAL* | | |
| = 68-60°C | | |

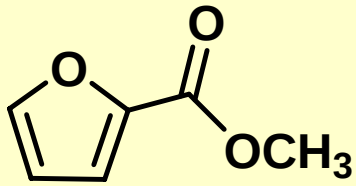


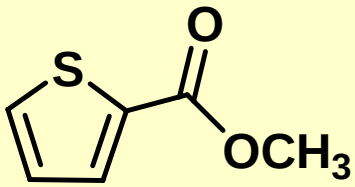
# MICROWAVE NITRONIUM TRIFLATE SCREENING REACTIONS

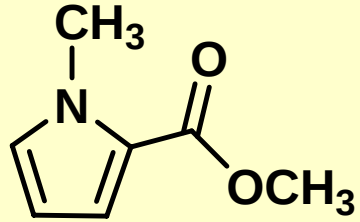
## ➢ 5-MEMBERED HETEROAROMATICS (ONE HETEROATOM)

- **DIFFERENT HETEROCYCLE REACTIVITY (Z = O, S, N)**



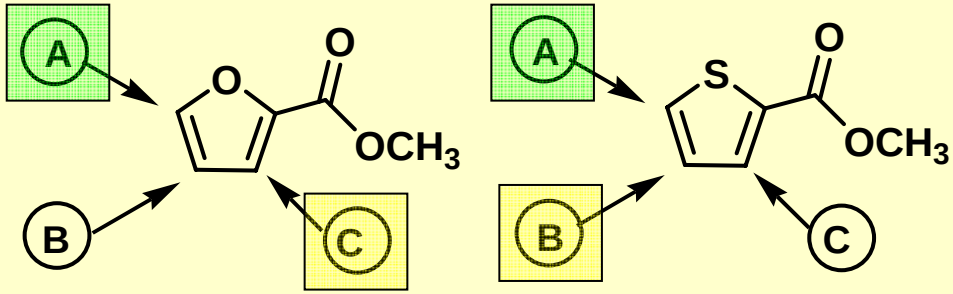




| | | |
|---|---|---|
| **REACTIVE AT RT** | **----------** | **VERY REACTIVE AT RT** |
| **NON-REACTIVE AT -78°C** | **NON-REACTIVE AT -78°C** | **VERY REACTIVE AT -78 °C** |

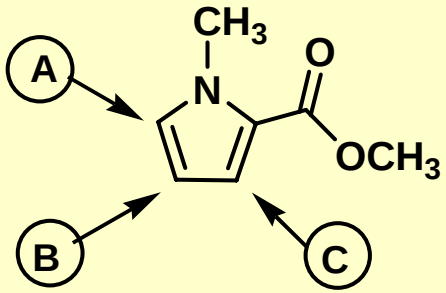
# MICROWAVE NITRONIUM TRIFLATE SCREENING REACTIONS

- **HETERO-RING DIRECTING EFFECTS**










| CONDITIONS | A | B | C | A | B | C |
|---|---|---|---|---|---|---|
| RT to 60°C MICROWAVE 1.1 M (5 MIN) | 95% | 0% | 5% | ---- | ---- | ---- |
| -78°C to 60°C MICROWAVE 0.7M (5 MIN) | 94% | 0% | 6%* | 59% | 36% | 5%(?) |
| | *2% UNREACTED | | | 62% | 38% | ---- |
| -78°C to RT CONVENTIONAL 0.7M (3 HR) | 97% | 0% | 3% | ---- | ----- | ---- |
| -78°C to RT CONVENTIONAL 0.09M (27-48 HRS) | 91-92% | 0 | 9-8% | 62% | 38% | 0% |

**NO NITRATED PRODUCT**

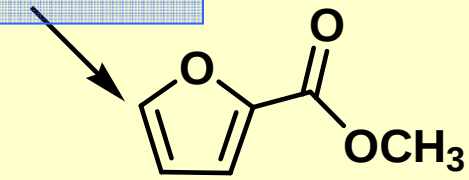
FURAN: SLIGHT CONC. EFFECT

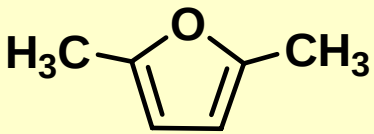
THIOPHENE: SLIGHT HEAT and./or CONC. EFFECT

# MICROWAVE NITRONIUM TRIFLATE SCREENING REACTIONS

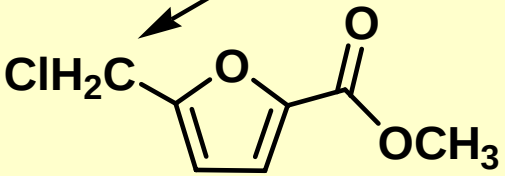
- **RING POSITIONAL REACTIVITY**

SELECTIVE -$NO_2$ POSITION



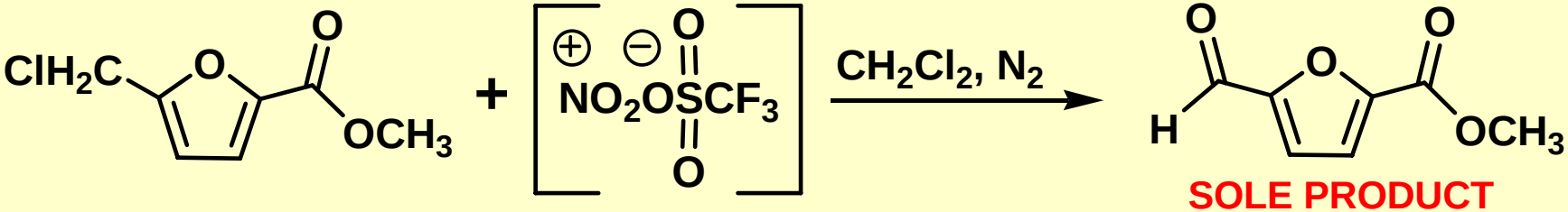


BENZYLIC-LIKE POSITION



**VERY** REACTIVE AT RT & -78°C, **NO** PRODUCT

**NON**-REACTIVE AT -78°C




**CONVENTIONAL** [0.19M, -78°C to RT, 76 HR]:

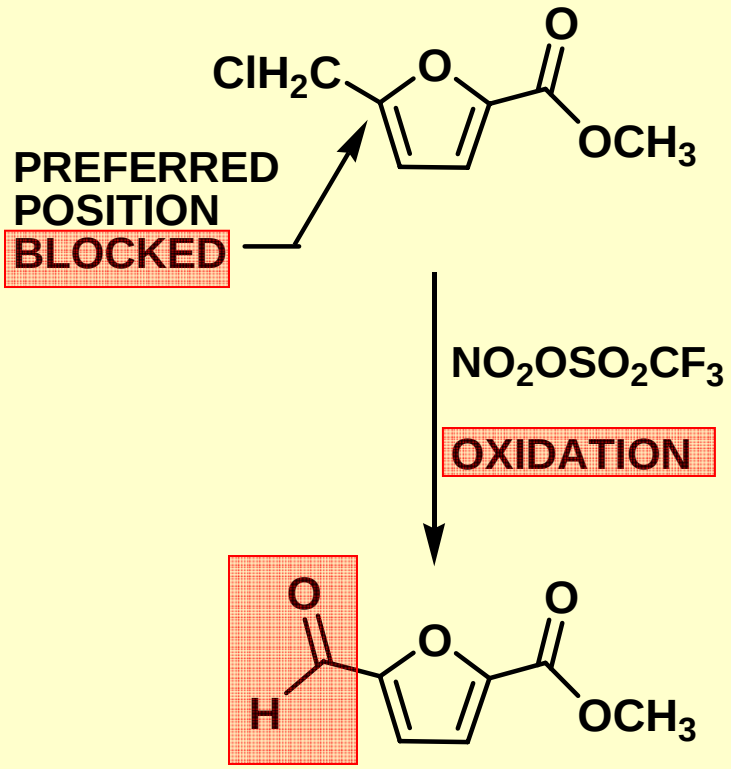
71% CONVERSION (NOT ISOLATED)

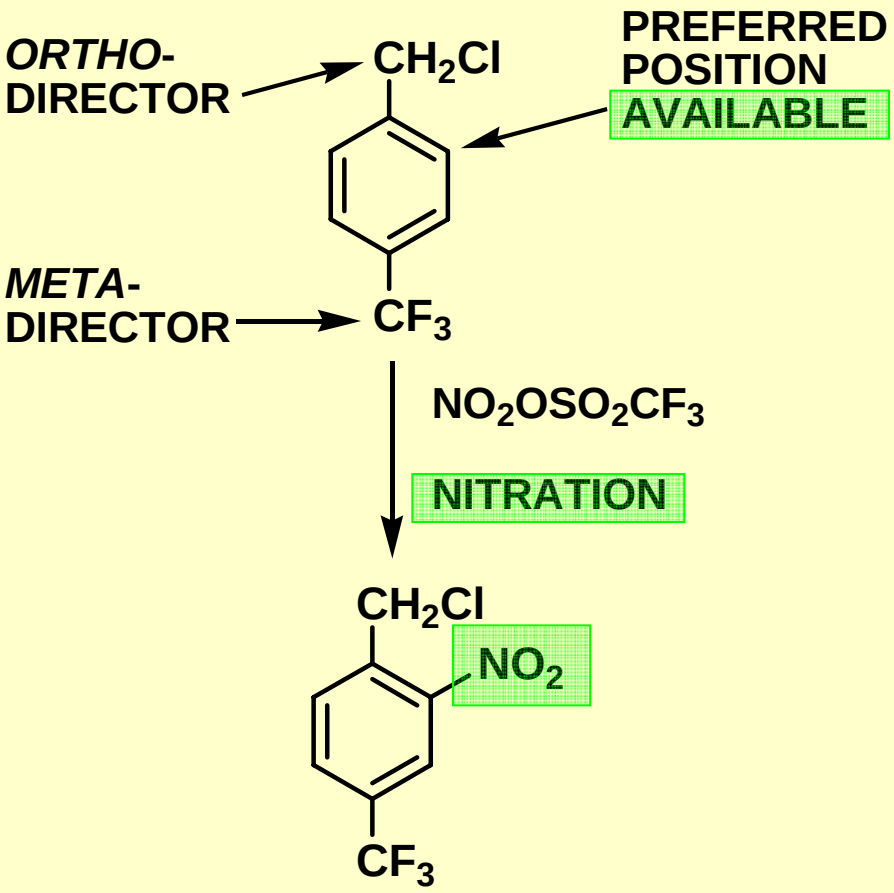
**MICROWAVE** [0.7M, -78°C to 70°C, 10 MIN]:

100% CONVERSION
64% YIELD (NMR PURE)
LT. YELLOW SOLID

# MICROWAVE NITRONIUM TRIFLATE SCREENING REACTIONS

- **RING POSITION REACTIVITY**

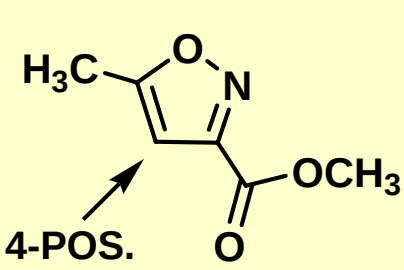


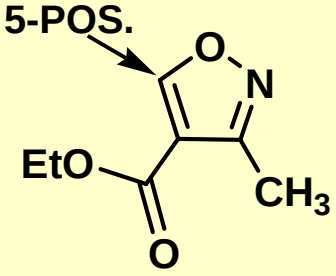
# MICROWAVE NITRONIUM TRIFLATE SCREENING REACTIONS

## ➢ 5-MEMBERED HETEROAROMATICS (TWO HETEROATOMS)

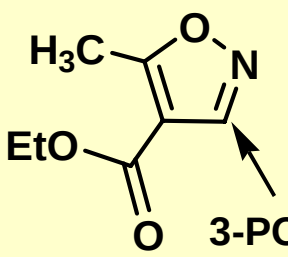
- 3,4,5-POSITION REACTIVITY PREFERENCE



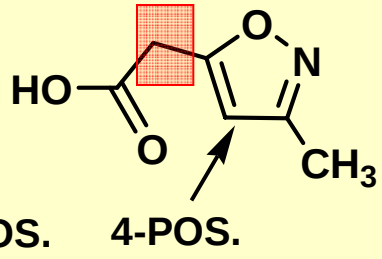

NON-REACTIVE AT RT
HIGH YIELD NITRATION
60°C, 5-15 MIN



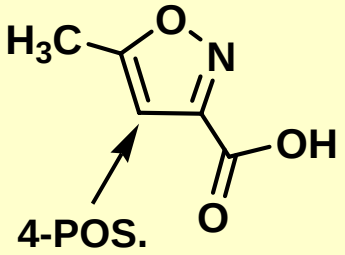

NON-REACTIVE AT RT
POSSIBLE TRACE NITRATON,
60-100°C, 6-10 MIN



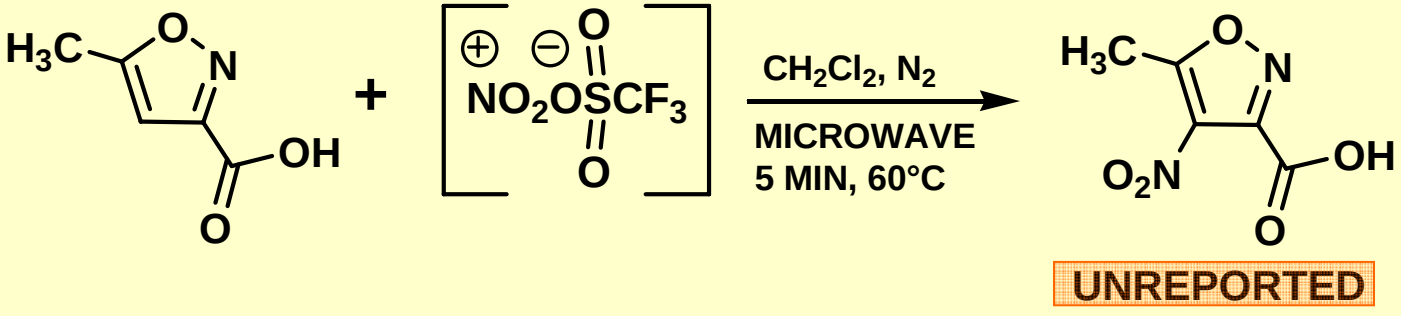

VERY REACTIVE AT RT
NON-REACTIVE AT -78°C
NO NITRATION




VERY REACTIVE AT -78°C
NO NITRATION OBSERVED




SEE BELOW




UNREPORTED

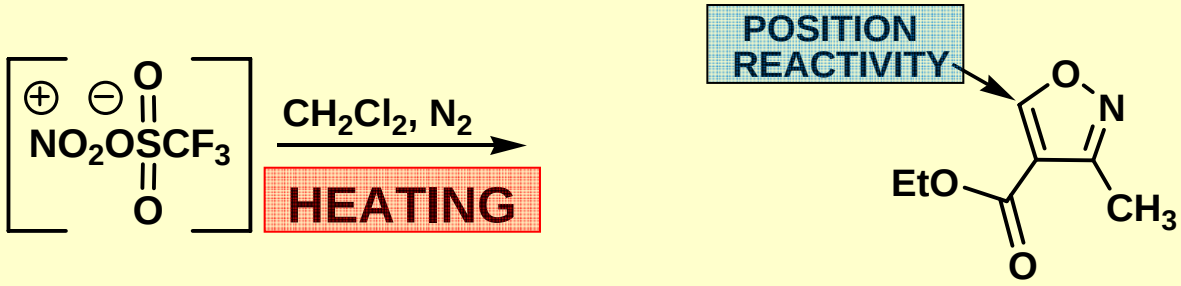
YELLOW SOLID
20+% CRUDE YIELD
NMR PURE

RECRYST. HOT $CH_2Cl_2$
WHITE SOLID

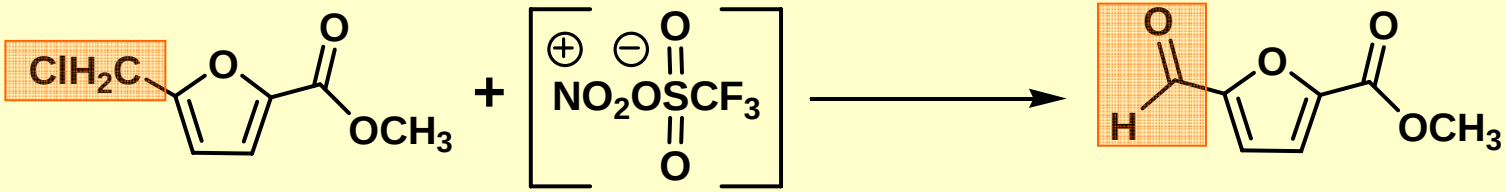
# SUMMARY

## ➢ MICROWAVE-ASSISTED SYNTHESIS A USEFUL TOOL

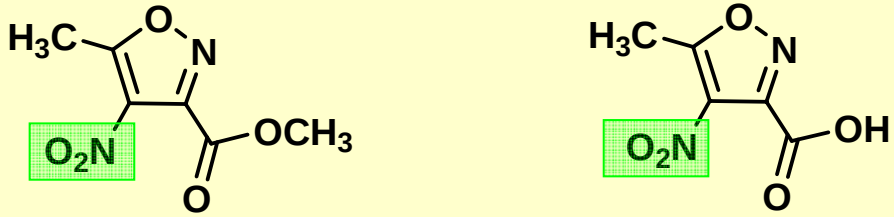
- **SCREENING NITRONIUM TRIFLATE NITRATION SAFETY / REACTIVITY**




- **COMPLETING NEW NITRONIUM TRIFLATE REACTION PATHWAY**




- **OBTAINING NOVEL NITRO-HETEROAROMATICS w. NITRONIUM TRIFLATE**



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